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<b>(54) Title:</b> MOISTURIZING COMPOSITIONS  <b>(57) Abstract</b>  The invention relates to skin moisturizing and conditioning compositions and methods. It is particularly concerned with the stimulation of ceramide production in the epidermis, leading to an increase in the level of these lipid materials in the stratum comeum of the skin , further leading to improved skin moisturization.		

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## MOISTURIZING COMPOSITIONS

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### FIELD OF THE INVENTION

The invention relates to skin moisturizing and conditioning compositions and methods. It is particularly concerned with the stimulation of ceramide production in the epidermis, leading to an increase in the level of these lipid materials in the stratum corneum of the skin, further leading to improved skin moisturization.

10

### BACKGROUND OF THE INVENTION

The stratum corneum, the outermost layer of the mammalian skin, contains intercellular lipids consisting predominately of ceramides, cholesterol and fatty acids. From studies involving lipid depletion of the stratum corneum by solvent extraction and from enzyme inhibition studies, ceramide, in particular, has been shown to be essential for the barrier function of the stratum corneum.

In normal skin, when there is disruption of the barrier function, the epidermis re-synthesizes the deficient lipids by inducing the expression or activation of the appropriate enzymes. However, under certain conditions, the skin's capacity for re-synthesis may be reduced. This is especially so in elderly subjects where the stratum corneum ceramide level is reportedly lower than that of younger subjects.

Attempts have been made to replace or augment the skin's normal ceramide barrier by directly applying natural or synthetic ceramide to the skin. Although such attempts have proved effective, they tend to suffer from short durations of action. Furthermore, such methods fail to account for the differences in delivery into the skin due to various skin conditions.

Therefore, a need exists for compositions which activate and improve the normal synthesis of ceramide in mammalian skin. The consumer perceived benefits from such compositions are to be seen in the improvement of skin condition, namely eradication or reversal of skin aging including removal or age spots, keratoses, wrinkles, skin lines, blotches, blemishes, nodules, pigmented spots, coarse, rough and dry skin, together with improvements in skin barrier function leading to fewer

problems of skin sensitivity (generally, and reactivity to irritants specifically), photo-damaged skin, loss of stratum corneum flexibility, and skin tightness.

It has now been found that ceramide synthesis precursors, when used in combination with vitamin B<sub>3</sub> compounds such as niacinamide, provide improved ceramide synthesis.

It is therefore an object of the present invention to provide compositions which activate and increase the rate of ceramide synthesis.

It is a further object of the present invention to provide improved methods of skin moisturization by applying a safe and effective amount of a skin moisturizing composition comprising a vitamin B<sub>3</sub> compound and a ceramide precursor.

These and other objects will become readily apparent from the detailed description which follows.

### **SUMMARY OF THE INVENTION**

The present invention relates to skin moisturizing compositions comprising:

- a.) a safe and effective amount of a vitamin B<sub>3</sub> compound; and
- b.) from about 0.0001% to about 10% of a ceramide pathway intermediate or precursors thereof and mixtures thereof.

The present invention also relates to methods of moisturizing skin by applying a safe and effective amount of the skin moisturizing composition.

Unless otherwise indicated, all percentages and ratios used herein are by weight of the total composition. All weight percentages, unless otherwise indicated, are on an actives weight basis. All measurements made are at approximately 25°C, unless otherwise designated. The term "safe and effective amount" as used herein means an amount of a compound or composition sufficient to significantly induce a positive benefit, preferably a positive skin appearance or feel benefit, including independently the benefits disclosed herein, but low enough to avoid serious side effects, i.e., to provide a reasonable benefit to risk ratio, within the scope of sound judgment of the skilled artisan.

### **DETAILED DESCRIPTION OF THE INVENTION**

The skin moisturizing compositions of the present invention can comprise, consist of, or consist essentially of the essential elements and limitations of the

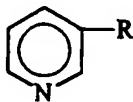
invention described herein, as well any of the additional or optional ingredients, components, or limitations described herein.

### ESSENTIAL COMPONENTS

#### Vitamin B<sub>3</sub> component

5       The compositions of the present invention comprise a safe and effective amount of a natural or synthetic vitamin B<sub>3</sub> compound. The compositions of the present invention preferably comprise from about 0.01% to about 50%, more preferably from about 0.1% to about 40%, even more preferably from about 0.1% to about 20%, and still more preferably from about 1% to about 20%, most preferably  
10       from about 1% to about 10%, of the vitamin B<sub>3</sub> compound .

As used herein, "vitamin B<sub>3</sub> compound" means a compound having the formula:



wherein R is - CONH<sub>2</sub> (i.e., niacinamide), - COOH (i.e., nicotinic acid) or - CH<sub>2</sub>OH  
15       (i.e., nicotinyl alcohol); derivatives thereof; and salts of any of the foregoing.

Exemplary derivatives of the foregoing vitamin B<sub>3</sub> compounds include nicotinic acid esters, including non-vasodilating esters of nicotinic acid, nicotinyl amino acids, nicotinyl alcohol esters of carboxylic acids, nicotinic acid N-oxide and niacinamide N-oxide.

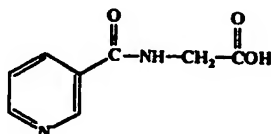
20       Suitable esters of nicotinic acid include nicotinic acid esters of C<sub>1</sub>-C<sub>22</sub>, preferably C<sub>1</sub>-C<sub>16</sub>, more preferably C<sub>1</sub>-C<sub>6</sub> alcohols. The alcohols are suitably straight-chain or branched chain, cyclic or acyclic, saturated or unsaturated (including aromatic), and substituted or unsubstituted. The esters are preferably non-rubifacient. As used herein, "non-rubifacient" means that the ester does not  
25       commonly yield a visible flushing response after application to the skin in the subject compositions (the majority of the general population would not experience a visible flushing response, although such compounds may cause vasodilation not visible to the naked eye). Alternatively, a nicotinic acid material which is rubifacient at higher doses could be used at a lower dose to reduce the rubifacient effect. Non-rubifacient esters

of nicotinic acid include tocopherol nicotinate and inositol hexanicotinate; tocopherol nicotinate is preferred.

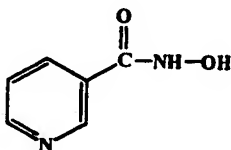
Other derivatives of the vitamin B<sub>3</sub> compound are derivatives of niacinamide resulting from substitution of one or more of the amide group hydrogens.

- 5 Nonlimiting examples of derivatives of niacinamide useful herein include nicotinyl amino acids, derived, for example, from the reaction of an activated nicotinic acid compound (e.g., nicotinic acid azide or nicotinyl chloride) with an amino acid, and nicotinyl alcohol esters of organic carboxylic acids (e.g., C1 - C18). Specific examples of such derivatives include nicotinuric acid and nicotinyl hydroxamic acid, which have the following chemical structures:

10 nicotinuric acid:



nicotinyl hydroxamic acid:



15

- Exemplary nicotinyl alcohol esters include nicotinyl alcohol esters of the carboxylic acids salicylic acid, acetic acid, glycolic acid, palmitic acid and the like. Other non-limiting examples of vitamin B<sub>3</sub> compounds useful herein are 2-chloronicotinamide, 6-aminonicotinamide, 6-methylnicotinamide, n-methyl-
- 20 nicotinamide, n,n-diethylnicotinamide, n-(hydroxymethyl)-nicotinamide, quinolinic acid imide, nicotinilide, n-benzylnicotinamide, n-ethylnicotinamide, nifenazone, nicotinaldehyde, isonicotinic acid, methyl isonicotinic acid, thionicotinamide, nialamide, 1-(3-pyridylmethyl) urea, 2-mercaptonicotinic acid, nicomol, and niaprazine.

- 25 Examples of the above vitamin B<sub>3</sub> compounds are well known in the art and are commercially available from a number of sources, e.g., the Sigma Chemical

Company (St. Louis, MO); ICN Biomedicals, Inc. (Irvin, CA) and Aldrich Chemical Company (Milwaukee, WI).

One or more vitamin B<sub>3</sub> compounds may be used herein. Preferred vitamin B<sub>3</sub> compounds are niacinamide and tocopherol nicotinate. Niacinamide is more preferred.

When used, salts, derivatives, and salt derivatives of niacinamide are preferably those having substantially the same efficacy as niacinamide in the methods of regulating skin condition described herein.

Salts of the vitamin B<sub>3</sub> compound are also useful herein. Nonlimiting examples of salts of the vitamin B<sub>3</sub> compound useful herein include organic or inorganic salts, such as inorganic salts with anionic inorganic species (e.g., chloride, bromide, iodide, carbonate, preferably chloride), and organic carboxylic acid salts (including mono-, di- and tri- C1 - C18 carboxylic acid salts, e.g., acetate, salicylate, glycolate, lactate, malate, citrate, preferably monocarboxylic acid salts such as acetate). These and other salts of the vitamin B<sub>3</sub> compound can be readily prepared by the skilled artisan, for example, as described by W. Wenner, "The Reaction of L-Ascorbic and D-Isoascorbic Acid with Nicotinic Acid and Its Amide", J. Organic Chemistry, VOL. 14, 22-26 (1949), which is incorporated herein by reference. Wenner describes the synthesis of the ascorbic acid salt of niacinamide.

In a preferred embodiment, the ring nitrogen of the vitamin B<sub>3</sub> compound is substantially chemically free (e.g., unbound and/or unhindered), or after delivery to the skin becomes substantially chemically free ("chemically free" is hereinafter alternatively referred to as "uncomplexed"). More preferably, the vitamin B<sub>3</sub> compound is essentially uncomplexed. Therefore, if the composition contains the vitamin B<sub>3</sub> compound in a salt or otherwise complexed form, such complex is preferably substantially reversible, more preferably essentially reversible, upon delivery of the composition to the skin. For example, such complex should be substantially reversible at a pH of from about 5.0 to about 6.0. Such reversibility can be readily determined by one having ordinary skill in the art.

More preferably the vitamin B<sub>3</sub> compound is substantially uncomplexed in the composition prior to delivery to the skin. Exemplary approaches to minimizing or preventing the formation of undesirable complexes include omission of materials which form substantially irreversible or other complexes with the vitamin B<sub>3</sub> compound, pH adjustment, ionic strength adjustment, the use of surfactants, and  
5 formulating wherein the vitamin B<sub>3</sub> compound and materials which complex therewith are in different phases. Such approaches are well within the level of ordinary skill in the art.

Thus, in a preferred embodiment, the vitamin B<sub>3</sub> compound contains a limited  
10 amount of the salt form and is more preferably substantially free of salts of a vitamin B<sub>3</sub> compound. Preferably the vitamin B<sub>3</sub> compound contains less than about 50% of such salt, and is more preferably essentially free of the salt form. The vitamin B<sub>3</sub> compound in the compositions hereof having a pH of from about 4 to about 7 typically contain less than about 50% of the salt form.

15 The vitamin B<sub>3</sub> compound may be included as the substantially pure material, or as an extract obtained by suitable physical and/or chemical isolation from natural (e.g., plant) sources. The vitamin B<sub>3</sub> compound is preferably substantially pure, more preferably essentially pure.

Without being limited by theory, it is believed that vitamin B<sub>3</sub> compounds  
20 such as niacinamide serve as precursors to such enzyme co-factors as nicotinamide adenine nucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP) and their reduced forms (NADH and NADPH). These co-factors provide the metabolic energy for synthesis of cellular components. For example, NADPH is a co-factor in the biosynthesis of fatty acids and sphinganine, two precursors to  
25 ceramides. NADPH is also believed to be an essential component of the cell for maintaining the cell's energy balance or reducing capacity, which is essential for normal cellular metabolic activity, including synthesis of biomolecules such as ceramides.

### 30 Ceramide Pathway Intermediates or Precursors



Another essential component of the present invention are the ceramide pathway intermediates or precursors. Ceramide pathway intermediates or precursors are discussed in detail in U.S. Patents 5,578,641 to Simon et al. and U.S. Patent 5,610, 040 to Smeets et al., both of which are herein incorporated by reference.

- 5 Without being limited by theory, it is believed the ceramide pathway intermediates or precursors serve to potentiate the ceramide synthesis properties of vitamin B<sub>3</sub> compounds to an extent greater than that of vitamin B<sub>3</sub> compounds alone

- Suitable ceramide pathway intermediates or precursors include, but are not limited to, serine, preferably L-serine; 3-dehydrosphinganine; sphinganine; 10 sphingosine; fatty acid amides; palmitoyl co-enzyme A; their natural and synthetic analogs and derivatives; or combinations thereof. The ceramide pathway intermediates or precursors are preferably present at a concentration of from about 0.0001% to about 10%, more preferably from about 0.01% to about 5% , and most preferably from about 0.1% to about 2%.

- 15 Ceramide pathway intermediates or precursors are commercially available from a number of sources, e.g., Sigma Chemical Co., St. Louis, MO.

## OPTIONAL COMPONENTS

### Ceramide Synthesis Co-factors

The compositions of the present invention may, optionally, include ceramide synthesis co-factors. Without being bound by specific theory or hypothesis, ceramide synthesis co-factors are molecules that are necessary for the biochemical reactions in ceramide synthesis to proceed but are not themselves converted into ceramides. Co-factors can often be rate-limiting in a biosynthetic process, particularly in older skin. Combining such co-factors with vitamin B<sub>3</sub>, thus, potentiates the ceramide synthesis properties of vitamin B<sub>3</sub> compounds. Non-limiting examples include pyridoxal, pyridoxine, pyridoxamine, riboflavin, pantothenic acid, co-enzyme A, acetyl co-enzyme A, flavin adenine dinucleotide (FAD), reduced FAD (FADH<sub>2</sub>), NAD, NADH, NADP, NADPH, their natural and synthetic analogs and derivatives, or mixtures thereof. The ceramide synthesis co-factors are preferably present at a concentration of from about 0.0001% to about 10%, more preferably from about 0.01% to about 5%, and most preferably from about 0.1% to about 2%.

Ceramide synthesis co-factors useful in the present invention are commercially available from a number of sources, e.g., Sigma Chemical Co., St. Louis, MO.

### Enzyme Inhibitors

The compositions of the present invention may also include enzyme inhibitors. Suitable enzyme inhibitors include neutral detergents (non-ionic surfactants), fatty acids, phosphatidyl choline, sphingomyelin, and N-oleylethanol amine. Without being limited by theory, it is also believed that the enzyme inhibitors of the present invention retard the enzymatic degradation of the ceramide barrier and, thus, facilitate the production of the ceramide barrier when combined with vitamin B<sub>3</sub> compounds. The enzyme inhibitors are preferably present at a concentration of from about 0.0001% to about 10%, more preferably from about 0.01% to about 5%, and most preferably from about 0.1% to about 2%.

Enzyme inhibitors useful in the present invention are commercially available from a number of sources, e.g., Sigma Chemical Co., St. Louis, MO.

### Carrier

The compositions of the present invention may optionally contain a dermatologically acceptable carrier. The phrase "dermatologically-acceptable carrier", as used herein, means that the carrier is suitable for topical application to the skin, has good aesthetic properties, is compatible with the actives of the present invention and any other components, and will not cause any untoward safety or toxicity concerns. A safe and effective amount of carrier is from about 50% to about 99.99%, preferably from about 99.9% to about 80%, more preferably from about 98% to about 90%, most preferably from about 95% to 90% of the composition.

The carrier can be in a wide variety of forms. For example, emulsion carriers, including, but not limited to, oil-in-water, water-in-oil, water-in-oil-in-water, and oil-in-water-in-silicone emulsions, are useful herein. These emulsions can cover a broad range of viscosities, e.g, from about 100 cps to about 200,000 cps. These emulsions can also be delivered in the form of sprays using either mechanical pump containers or pressurized aerosol containers using conventional propellants. These carriers can also be delivered in the form of a mousse. Other suitable topical carriers include anhydrous liquid solvents such as oils, alcohols, and silicones (e.g., mineral oil, ethanol, isopropanol, dimethicone, cyclomethicone, and the like); aqueous-based single phase liquid solvents (e.g., hydro-alcoholic solvent systems); and thickened versions of these anhydrous and aqueous-based single phase solvents (e.g., where the viscosity of the solvent has been increased to form a solid or semi-solid by the addition of appropriate gums, resins, waxes, polymers, salts, and the like). Examples of topical carrier systems useful in the present invention are described in the following four references all of which are incorporated herein by reference in their entirety: "Sun Products Formulary" Cosmetics & Toiletries, vol. 105, pp. 122-139 (December 1990); "Sun Products Formulary", Cosmetics & Toiletries, vol. 102, pp. 117-136 (March 1987); U.S. Patent No. 4,960,764 to Figueroa et al., issued October 2, 1990; and U.S. Patent No. 4,254,105 to Fukuda et al., issued March 3, 1981.

The carriers of the skin care compositions can comprise from about 50% to about 99% by weight of the compositions of the present invention, preferably from about 75% to about 99%, and most preferably from about 85% to about 95%.

Preferred cosmetically and/or pharmaceutically acceptable topical carriers  
5 include hydro-alcoholic systems and oil-in-water emulsions. When the carrier is a hydro-alcoholic system, the carrier can comprise from about 0% to about 99% of ethanol, isopropanol, or mixtures thereof, and from about 1% to about 99% of water. More preferred is a carrier comprising from about 5% to about 60% of ethanol, isopropanol, or mixtures thereof, and from about 40% to about 95% of water.  
10 Especially preferred is a carrier comprising from about 20% to about 50% of ethanol, isopropanol, or mixtures thereof, and from about 50% to about 80% of water. When the carrier is an oil-in-water emulsion, the carrier can include any of the common excipient ingredients for preparing these emulsions. A more detailed discussion of suitable carriers is found in U.S. Patent 5,605,894 to Blank et al., and in PCT  
15 application WO 97/39733, published October 30, 1997, to Oblong et al., both herein incorporated by reference in their entirety.

The moisturizing compositions of the present invention may optionally comprise additional skin actives. Non-limiting examples of such skin actives include hydroxy acids such as salicylic acid; desquamatory agents such as zwitterionic  
20 surfactants; sunscreens such as 2-ethylhexyl-p-methoxycinnamate, 4,4'-t-butyl methoxydibenzoyl-methane, octocrylene, phenyl benzimidazole sulfonic acid; sun-blocks such as zinc oxide and titanium dioxide; anti-inflammatory agents; anti-oxidants/radical scavengers such as tocopherol and esters thereof; metal chelators, especially iron chelators; retinoids such as retinol, retinyl palmitate, retinyl acetate,  
25 retinyl propionate, and retinal; N-acetyl-L-cysteine derivatives; benzofuran derivatives; and skin protectants. Mixtures of any of the above mentioned skin actives may also be used. A more detailed description of these actives is found in U.S. Patent 5,605,894 to Blank et al. (previously incorporated by reference). Preferred skin actives include hydroxy acids such as salicylic acid, sunscreen ,  
30 antioxidants and mixtures thereof.

Other conventional skin care product additives may also be included in the compositions of the present invention. For example, urea, guanidine, glycerol, petrolatum, mineral oil, sugar esters and polyesters, polyolefins, methyl isostearate, ethyl isostearate, cetyl ricinoleate, isononyl isononanoate, isohexadecane, lanolin, lanolin esters, cholesterol, pyrrolidone carboxylic acid/salt (PCA), trimethyl glycine (betaine), tranexamic acid, amino acids (e.g., serine, alanine) and/or their salts, panthenol and its derivatives, collagen, hyaluronic acid, elastin, hydrolysates, primrose oil, jojoba oil, epidermal growth factor, soybean saponins, mucopolysaccharides, and mixtures thereof may be used. Other suitable additives or skin actives are discussed in further detail in PCT application WO 97/39733, published October 30, 1997, to Oblong et al., herein incorporated by reference in its entirety.

#### **Preparation of Skin Moisturizing Compositions**

The compositions of the present invention are generally prepared by conventional methods such as are known in the art of making topical compositions. Such methods typically involve mixing of the ingredients in one or more steps to a relatively uniform state, with or without heating, cooling, application of vacuum, and the like. Non-limiting examples of the product form can be a gel, emulsion, lotion, cream, ointment, solution, liquid, etc.

#### **Methods of Moisturizing Skin**

The methods of the present invention are useful for moisturizing mammalian skin (especially human skin, more especially human facial skin), especially the epidermis and more especially the stratum corneum of mammalian skin. The skin moisturization methods of the present invention involve topically applying to the skin a safe and effective amount of the skin moisturizing composition of the present invention. The amount of the composition which is applied, the frequency of application and the period of use will vary widely depending upon the level of vitamin B<sub>3</sub> compound and/or other components of a given composition and the level of moisturization desired.

In a preferred embodiment, the composition is chronically applied to the skin. By "chronic topical application" is meant continued topical application of the composition over an extended period during the subject's lifetime, preferably for a period of at least about one week, more preferably for a period of at least about two weeks, even more preferably for a period of at least one month, even more preferably for at least about three months, even more preferably for at least about six months, and more preferably still for at least about one year. While benefits are obtainable after various maximum periods of use (e.g., five, ten or twenty years), it is preferred that chronic application continue throughout the subject's lifetime to maintain and/or increase the benefits achieved. Typically applications would be on the order of one to four times per day over such extended periods, however application rates can be more than four times per day, especially for use on particularly dry skin-prone areas of the body such as the hands and legs.

A wide range of quantities of the compositions of the present invention can be employed to provide a skin appearance and/or feel benefit. Quantities of the present compositions which are typically applied per application are, in mg composition/cm<sup>2</sup> skin, from about 0.1 mg/cm<sup>2</sup> to about 10 mg/cm<sup>2</sup>. A particularly useful application amount is about 2 mg/cm<sup>2</sup>.

Regulating skin condition is preferably practiced by applying a composition in the form of a skin lotion, cream, gel, cosmetic, or the like which is intended to be left on the skin for some esthetic, prophylactic, therapeutic or other benefit (i.e., a "leave-on" composition). After applying the composition to the skin, it is preferably left on the skin for a period of at least about 15 minutes, more preferably at least about 30 minutes, even more preferably at least about 1 hour, most preferably for at least several hours, e.g., up to about 12 hours.

Another approach to ensure a continuous exposure of the skin to at least a minimum level of vitamin B3 compound is to apply the compound by use of a patch. Such an approach is particularly useful for problem skin areas needing more intensive treatment. The patch can be occlusive, semi-occlusive or non-occlusive. The vitamin B3 compound composition can be contained within the patch or be applied to the skin prior to application of the patch. The patch can also include additional actives

such as chemical initiators for exothermic reactions such as those described in PCT application WO 9701313 to Burkett et al. Preferably the patch is applied at night as a form of night therapy.

5

### EXAMPLES

The following examples further describe and demonstrate embodiments within the scope of the present invention. The examples are given solely for the purpose of illustration and are not to be construed as limitations of the present invention, as many variations thereof are possible without departing from the spirit and scope of the invention.

10

#### Example 1

A skin cream is prepared by conventional methods from the following components.

	Ingredient (CTFA Name)	Weight %
PHASE A:	Water U.S.P.	57.31
	Disodium EDTA	0.13
	Methyl Paraben	0.25
	Glycerin	3.00
	Zinc Citrate	1.00
PHASE B:	Cetyl Alcohol	0.56
	Stearyl Alcohol	2.03
	Behenyl Alcohol	0.22
	Steareth-21 (Brij 721)	0.37
	Steareth-2 (Brij 72)	1.10
	Distearyldimonium chloride (Varisoft TA-100)	0.95
	Propyl Paraben	0.10
	Polypropylene glycol-15 stearyl ether (Arlamol E)	3.25
PHASE C:	Polypropylene glycol-15 stearyl ether (Arlamol E)	2.17
	Titanium dioxide	0.75
PHASE D:	Niacinamide	5.00
	Citric acid	0.19

	L-serine	1.00
	Water U.S.P.	16.00
	50% NaOH	0.94
PHASE E:	Benzyl Alcohol	0.50
	Silicone fluid (Dow Corning DC Q2 - 1401; cyclomethicone/dimethiconol - 50/50 blend)	0.75
	Dimethicone 10 cst (Dow Corning)	1.00
	Polyethylene Low Density Beads	1.00
PHASE F:	Fragrance	0.10
PHASE G:	50% NaOH	0.33

Blend the A phase components with a suitable mixer (e.g., Tekmar model RW20DZM), heating while stirring to a temperature of 70-80°C. Separately, blend the B phase components with a suitable mixer and heat with mixing to melt the components. Separately, blend the C phase components and mill to obtain an acceptably smooth mixture (e.g., using a Tekmar T50 Mill).

Add the C phase mixture to the B phase mixture and mix. Then add the resulting mix to the A phase mixture with mixing, cool with a cold water bath and mill, then continue stirring. Remove the combination from the bath, with continued stirring, once the temperature reaches 40°C.

Separately, blend the D phase components by stirring until dissolved, then add this to the combination of A-C materials.

Separately, blend the E phase components by mixing until smooth and continuous, then add this to the combination of the A-D materials. Add and mix the fragrance, then the NaOH. Adjust the pH as necessary to 5.5.

Apply the composition to a subject's dry skin at the rate of 2 mg composition/cm<sup>2</sup> skin once or twice daily for a period of at least 3-6 months to improve moisturization of the skin.

### Example 2

An emulsion is prepared by conventional methods from the following components:

Ingredient	Weight %
Silicone fluid (Dow Corning DC 345)	15.0
Silicone fluid (Dow Corning DC 3225C)	2.5
Silicone fluid (Goldschmidt Abil We09)	2.5
Water	72.4
Tocopherol nicotinate	2.0



L-serine	1.0
pyridoxine	1.0
Tetrasodium EDTA	0.1
Benzyl alcohol	0.3
Methyl paraben	0.2
Glycerin	3.0

Form the water phase in a suitable vessel charged with the water as follows: add the glycerin and then niacinamide to the water with stirring. Add to this mixture with stirring the methyl paraben dissolved in the benzyl alcohol. Add to this mixture with stirring the EDTA.

- 5 Form the silicone phase in a separate suitable vessel by adding and stirring together the silicone fluids.

Add the water phase to the silicone phase slowly with stirring to form the emulsion.

- 10 Apply the resulting composition to a subject's dry skin at the rate of 2 mg composition/cm<sup>2</sup> skin once or twice daily for a period of at least 3-6 months to improve moisturization.

### Example 3

A skin cream is prepared by conventional methods from the following components.

	Ingredient (CTFA Name)	Weight %
PHASE A:	Water U.S.P.	62.96
	Disodium EDTA	0.15
	Glycerin	5
PHASE B:	Cetyl hydroxy ethyl cellulose	0.15
	Methyl Paraben	0.25
PHASE C:	Cetyl Alcohol	0.5
	Stearyl Alcohol	0.5
	Behenyl Alcohol	0.5
	Cetyl ricinoleate	3
	Steareth-2 (Brij 72)	1.05
	Distearyldimonium chloride (Varisoft TA-100)	0.25
	Propyl Paraben	0.10
	Myristyl myristate	1.5
	Caprylic/Capritryglycerides	1.5
	Mineral oil	2

	Fatty acid ester of sugar*	1
	Polypropylene glycol-15 stearyl ether (Arlamol E)	1.05
PHASE D:	Dimethicone 10 cst (Dow Corning)	2
PHASE E:	Niacinamide	5
	Pyridoxine	0.5
	Pantothenic acid	0.5
	Water U.S.P.	10
PHASE F:	Benzyl Alcohol	0.5
PHASE G:	50% NaOH	0.04

- \* A C1-C30 monoester or polyester of sugars and one or more carboxylic acid moieties as described herein, preferably a sucrose polyester in which the degree of esterification is 7-8, and in which the fatty acid moieties are C18 mono- and/or di-unsaturated and behenic, in a molar ratio of unsaturates:behenic of 1:7 to 3:5, more preferably the octaester of sucrose in which there are about 7 behenic fatty acid moieties and about 1 oleic acid moiety in the molecule, e.g., sucrose ester of cottonseed oil fatty acids.

Blend the A phase components with a suitable mixer (e.g., Tekmar model RW20DZM), heating while stirring to a temperature of about 70-80°C. Add the cetyl hydroxy ethyl cellulose and methyl paraben with mixing at about 70-80°C to melt the components. Separately, blend the C phase components and mill to obtain an acceptably smooth mixture (e.g., using a Tekmar T50 Mill).

Add the C phase mixture to the above mixture and mix. Remove the combination from the bath, with continued stirring, once the temperature reaches about 45°C. Add the dimethicone and mix.

Separately, blend the E phase components by mixing until smooth and continuous, then add this to the above mixture. Add and mix in the benzyl alcohol, then the NaOH. Adjust the pH as necessary to 7.

Apply the composition to a subject's dry skin at the rate of 2 mg composition/cm<sup>2</sup> skin once or twice daily for a period of at least 3-6 months to improve moisturization.

#### Example 4

A skin cream is prepared by conventional methods from the following components.

	Component	Weight %
PHASE A:	Benzyl alcohol	0.30

	Methyl p-hydroxybenzoate (a.k.a. methylparaben)	0.20
	Ethanol	3.00
PHASE B:	Water	60.10-60.85
	Disodium EDTA	0.50
	Glycerol	10.00
	Hexylene glycol	2.00
	Niacinamide	2.00
	linoleoyl amide	0.501.00
	Triethanol amine	0.05
	Butylated hydroxytoluene	0.10
PHASE C:	Silicone fluid (Dow Corning DC 345)	12.50
	Silicone fluid (Goldschmidt Abil We-09)	2.50
	Silicone fluid (Dow Corning DC 3225C)	2.50
	Petrolatum	1.50
	Retinol (10% in soybean oil)	0.75-1.50
	Fatty acid ester of sugar*	1.00

\* See Example 3

Blend the A phase components with a suitable mixer (e.g., Tekmar model RW20DZM). Blend the B phase components into the A phase with a suitable mixer. Separately, blend the C phase components until they are uniform. Add the C phase mixture to the A/B phase mixture, mix until uniform and emulsified, and then mill to obtain an acceptably smooth mixture (e.g., using a Tekmar T50 Mill).

Apply the composition to a subject's dry skin at the rate of 2 mg composition/cm<sup>2</sup> skin once or twice daily for a period of at least 3-6 months to improve moisturization.

An alternative skin cream having reduced retinol levels can be prepared in the same manner from the above components wherein the retinol is added in an amount of 0.025% (0.25% of 10% retinol in soybean oil), quo sine to 100% with water, the amounts of the other components being as shown.

**WHAT IS CLAIMED IS:**

1. A skin moisturizing composition comprising:
  - a.) a safe and effective amount of a vitamin B<sub>3</sub> compound; and
  - b.) from 0.0001% to 10% of a ceramide pathway intermediate, precursor thereof or mixtures thereof.
2. A skin moisturizing composition according to Claim 1, wherein the ceramide intermediate or precursor is selected from the group consisting of L-serine, 3-dehydrosphinganine, sphinganine, sphingosine, fatty acid amides, palmitoyl co-enzyme A, derivatives thereof, and mixtures thereof.
3. A skin moisturizing composition according to any one of the preceding Claims, wherein the concentration of the vitamin B<sub>3</sub> compound is from 0.1% to 20%.
4. A skin moisturizing composition according to any one of the preceding Claims, wherein said vitamin B<sub>3</sub> compound is selected from niacinamide, derivatives of niacinamide, non-vasodilating esters of nicotinic acid, and mixtures thereof.
5. A skin moisturizing composition according to any one of the preceding Claims, further comprising a ceramide synthesis co-factor.
6. A skin moisturizing composition comprising:
  - a) a safe and effective amount of a vitamin B<sub>3</sub> compound; and
  - b) ceramide synthesis co-factor.

7. A skin moisturizing composition according to any one of the preceding Claims, wherein the ceramide synthesis co-factor is selected from the group consisting of pyridoxal, pyridoxine, pyridoxamine, riboflavin, pantothenic acid, co-enzyme A, acetyl co-enzyme A, flavin adenine dinucleotide, nicotinamide adenine nucleotide, nicotinamide adenine dinucleotide phosphate, reduced forms thereof, derivatives thereof, and mixtures thereof.
8. A skin moisturizing composition according to any one of the preceding Claims, wherein the concentration of the vitamin B<sub>3</sub> compound is from 0.1% to 20%.
9. A skin moisturizing composition according to any one of the preceding Claims, wherein said vitamin B<sub>3</sub> compound is selected from niacinamide, derivatives of niacinamide, non-vasodilating esters of nicotinic acid, and mixtures thereof.
10. A skin moisturizing composition according to any one of the preceding Claims, wherein said vitamin B<sub>3</sub> compound is selected from niacinamide, tocopherol nicotinate, and mixtures thereof.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/05409

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 A61K7/48

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 88 06034 A (FIASCHETTI MARY GEMMA) 25 August 1988 (1988-08-25) abstract; claims 1,6,8,9,11,12	1-9
X	CHEMICAL ABSTRACTS, vol. 128, no. 9, 2 March 1998 (1998-03-02) Columbus, Ohio, US; abstract no. 106240, XP002112190 & JP 10 001410 A (KANEBO LTD) 6 January 1998 (1998-01-06) abstract	1-5,8,9

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
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## INTERNATIONAL SEARCH REPORT

International Application No

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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